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(21) International Application Number: PCT/US92/00772 (22) International Filing Date: 29 January 1992 (29.01.92) (30) Priority data: 673,986 22 March 1991 (22.03.91) US (71) Applicants: LONZA INC. [US/US]; 17-17 Route 208, Fair Lawn, NJ 07410 (US). UNIVERSITY OF GEORGIA RESEARCH FOUNDATION, INC. [US/US]; 623 Boyd Graduate Studies Research Center, D. W. Brooks Drive, Athens, GA 30602 (US). KANSAS STATE UNIVERSITY RESEARCH FOUNDATION [US/US]; 146 Durland Hall, Kansas State University, Manhattan, KS 66506 (US). (72) Inventors: BLUM, Stephen, A. ; 930 29th Street, Des Moines, IA 50312 (US). GOODBAND, Robert, D. ; 2815 Illinois Lane, Manhattan, KS 66502 (US). NELSS-EN, Jim, L. ; 7234 Turtle Creek Blvd., Manhattan, KS 66502 (US). NEWTON, Larry, G. ; Rt. 6, Box 323, Tifton, GA 31794 (US).		(74) Agents: LEWEN, Bert, J. et al.; Darby & Darby, 805 Third Avenue, 27th Floor, New York, NY 10022 (US). (81) Designated States: AT (European patent), AU, BB, BE (European patent), BG, BR, CA, CH (European patent), DE (European patent), DK (European patent), ES (European patent), FI, FR (European patent), GB (European patent), GR (European patent), HU, IT (European patent), JP, KP, KR, LK, LU (European patent), MC (European patent), MG, MW, NL (European patent), NO, RO, RU, SD, SE (European patent). Published <i>With international search report.</i>
(54) Title: CARNITINE-SUPPLEMENTED DIET FOR STARTER PIGS (57) Abstract A feed composition containing L-carnitine and a high nutrient density diet is found to increase the lean-to-fat ratio of early weaned pigs. The L-carnitine is preferably reduced as the animal passes through its various stages of development, with initial concentrations ranging from 5 to 5000 ppm. In the finishing stage, less than 5 ppm of L-carnitine may advantageously be incorporated in the diet.		

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CARNITINE-SUPPLEMENTED DIET FOR STARTER PIGSBackground of the Invention

It has long been desirable to increase feed efficiency, weight gain, and lean tissue of swine. Work has been performed with carnitine to achieve certain of these results and some success has been achieved. G. L. Newton and K. D. Haydon reported in the 1986 University of Georgia Swine Report that feeding diets containing 0.95, 1.1 or 1.25% lysine, with or without 0.2% dl-carnitine HCl, to 28 day old nursery pigs had an effect on daily weight gains and feed efficiency. The pigs were fed a conventional diet containing 72.4% corn and 24.2% soybean meal with vitamin, mineral and antibiotic supplementation. The 1.1% lysine diet produced higher daily gains and improved feed efficiencies than the other diets. The effect on daily gain was significant throughout the study, while the effect on feed efficiency was significant for the first 4 days. There were also significant linear and curvilinear effects of lysine level on feed efficiency after 4 and 28 days. Carnitine did not have a significant effect on performance and did not alter the need for lysine. However, the results indicated the

possibility of a greater response to supplemental lysine when nursery diets were also supplemented with carnitine. There were indications that post-weaning lag might be somewhat reduced in lighter weight pigs.

5 The results of two supplemental trials conducted to determine whether addition of carnitine to nursery diets would have an effect on post-weaning lag were reported in the 1987 University of Georgia Swine Report by G. L. Newton and K. D. Haydon. In the first trial, 144 pigs were fed simple corn-soy
10 diets containing two levels of lysine and four levels of carnitine. For the other trial, 180 pigs 28 days of age were fed complex diets containing milk products and three levels of lysine and three levels of carnitine. When added to the simple
15 diet, carnitine tended to produce an increase in feed intake during the first 4 days, which resulted in slightly better gains and feed efficiency at that time. When added to the complex diet, carnitine tended to increase food intake over the entire 20 day trial. Carnitine addition resulted in increased weight gains at 14 and 20 days.

20 Work with L-carnitine in connection with finishing pigs has also been conducted. U.S. Patent Application, Ser. No. 387,856, filed July 31, 1989, improved weight gain, feed efficiency, and reduction of back fat were observed.

25 In addition, efforts have been made to decrease post-weaning "lag" which has become more of a problem as swine are weaned earlier and earlier. Research work has been directed towards a variety of nutritional programs for early weaned pigs (weaning from 14 to 21 days of age), including high nutrient-

density diets (J. L. Nelssen, "High Nutrient-Density Diets for Weanling Pigs," Kansas State University Swine Research Report 1986, pages 35 to 50). A major shortcoming of the foregoing work is that the feed regimes described did not appear to increase the lean tissue growth.

It has been reported that swine from different genetic sources (genotypes) have different capacities for lean tissue growth and that its disposition is affected by the availability of amino acids. In a 1989 University of Kentucky Research Report in an article by T. S. Stahly et al., "Influence of Genetic Capacity for Lean Tissue Growth on the Amino Acid Needs of Pigs," it was noted that carcass leanness was improved as dietary lysine levels were raised in connection with pigs in the 40 to 240 pound range and that pigs with high lean growth potential had much higher growth performance and lean gain when the nutrient density of the diet was increased. These results indicated that some improvement in lean growth, through dietary manipulation, should be possible with all genotypes.

Summary of the Invention

It has now been discovered that the feeding of early weaned pigs (often called "starter pigs"), in a timely manner, with a combination of L-carnitine and a high nutrient-density diet (HNDD) not only increases average weight gain and feed efficiency, but also unexpectedly increases the lean tissue growth in such animals. This result is particularly surprising because starter pigs are in a period of rapid growth where there is very little fat. (This is in contrast to finishing

pigs, where there is a much higher ratio of fat to lean.) Most strikingly, this increase in lean tissue is maintained through the later stages of growth of the pig. It is speculated that at this stage of the animal's development and with the HNDD, the L-carnitine actually partitions the nutrients so as to favor lean accretion, despite the already lean state of the animal, while at the same time allowing sufficient fat to form as is necessary for normal growth.

To be effective, it is necessary that the feed regimen be commenced at a time when the endogenous carnitine synthesis is very low, i.e., preferably in the period when the pig is less than about 24 days of age and when the pig is growing at or near its true genetic potential. The response to the carnitine-supplemented HNDD will, of course, be more pronounced for genotypes having high lean growth capacities.

Detailed Description of the Invention

In the practice of the invention, starter pigs from birth up to 24 days of age having an initial weight of from 3 to 16 pounds are fed the diet of the invention in at least two, preferably in three, phases. The Phase 1 diet is for a period of from one to three weeks, preferably two weeks or until the body weight is about 15 pounds, and contains from about 5 to 5000 ppm of L-carnitine, preferably about 500 to 2000 ppm, optimally about 1000 ppm.

In Phase 2, commenced when the pig is about 35 days old, the diet is administered from two to four weeks after Phase 1, preferably for three additional weeks. The L-car-

nitine is optimally reduced to 500 ppm, but amounts between 250 and 1000 ppm are also effective.

Even after Phase 2, the addition of L-carnitine as a feed supplement may be advantageous in both the grower stage (i.e., up to a weight of 160 pounds; approximately 130 days of age) and the finishing stage. During the grower stage (56 to 160 lb.), the amount of carnitine would be gradually reduced from 500 to 5 ppm. The maximum during finishing is 50 ppm, desirably from 5 to 50 ppm. Generally as the weight of the animal increases, the optimum amount of carnitine decreases.

As mentioned previously, early weaning often refers to weaning at 3 weeks of age or less. In modern nursery facilities, pigs are often weaned at 21 days of age onto an inferior diet, with pigs losing weight the first week postweaning. In fact, weaning at 3 weeks of age in commercial operations commonly results in nursery pigs ranging in age from 14 to 28 days. Obviously, early weaning results in several lightweight pigs

(<10 lb.) that require increased nutrient density and diet palatability to maintain growth on a dry diet. To provide optimum nutritional management for the early weaned pig, a three-phase starter program during the nursery phase of swine production was developed at Kansas State University. Listed below is a description of this starter program, with the suggested feeding interval for each phase.

Three-Phase Starter Program

<u>Item</u>	<u>Description</u>	<u>Recommendation</u>
Phase 1	High Nutrient-	Fed to pigs until body

	Density Diet	weight is at least 15 lb.
Phase 2	1.25% lysine, whey, corn-soybean diet	Fed to pigs from 15 to 25 lb.
5 Phase 3	1.10% lysine, grain- soybean diet	Fed to pigs until body weight is approx. 50 lb.

10 Starter diets for pigs weaned at 14 to 21 days of age
have been the topic of considerable speculation because of the
variation in results. Swine producers have grown accustomed to
seeing early-weaned pigs experience a postweaning "check",
which often results in increased days to market in their
15 production unit. In fact, many producers have replaced 21-day
weaning with a 28-day weaning program, simply because of the
adverse performance of pigs during the initial week in the
nursery. A high nutrient-density diet (HNDD) is a type of
milk-based diet that is intended to improve the initial starter
20 pig performance. Various formulations of HNDD have been tried
in commercial swine production units with variable success.

There are actually two types of HNDD that have been
formulated for early-weaned pigs. The first approach has been
to formulate diets to be as similar to sow's milk as possible,
25 but in a dry form. Diets based on total milk protein with
added vitamins and minerals are very successful, yet prohibi-
tively expensive. In a similar category is a HNDD formulated
with an understanding of the digestive capacity of the young
pig, but with some awareness for economic constraints. Such
30 HNDD diets, useful in the practice of the subject invention,
are described in the following Table:

Table: Characteristics of a Three-Phase Starter Program

5	<u>Item</u> <u>Weight</u>	Phase 1	Phase 2	Phase 3
		<u>HNDD</u>	<u>Whey Start</u>	<u>To 50 lb.</u> <u>B o d y</u>
10	Protein, %	20-25	18-20	18
	Lysine, %	1.5-1.6	1.25	1.10
	Added Fat, %	8-10	3-5	--
15	Dried Edible Whey, %	15-25	15-20	0-5
	Dried Skim Milk, %	10-25	--	--
	Fish Meal, %	0-3	3-5	--
20	Copper, ppm	190-260	190-260	190-260
	Vitamin E, IU/ton	40,000	40,000	40,000
	Selenium, ppm	.3	.3	.3
25	Antibacterial or Antibiotic	+	+	+
	Physical Form	1/8" Pellet	1/8" Pellet	Meal Form

As a general matter, the Phase 1 diets (which are supplemented with carnitine in accordance with the practice of the instant invention) contain at least 15%, preferably from 18 to 30%, protein; from 30 to 45% dried milk products such as light edible whey, dried skim milk, and casein; and from 5 to 15% added fat.

In Phase 2, the protein is decreased to less than 25%, preferably from 15 to 25%; the dried milk products to less than 25%, preferably from 10 to 25%; and the added fat to from about 1 to 5%.

In Phase 3, the diet maintains about the same percentage of protein as in Phase 2, the dried milk products are

reduced to less than 10%, and the added fat substantially eliminated.

While the term "milk products" is used in the above description, it should be understood that this term is intended to include nutritional products which are derived from other sources and have compositions substantially similar to those derived from milk. These include soy protein concentrates made by extracting soy flour with ethanol to reduce the carbohydrate content, soy isolates which further concentrate the protein by acid extracting soy flour with acid, and plasma protein which is obtained by the spray drying of porcine or bovine plasma. The essential factor is to obtain a protein source that has a solids content similar to that in the mother's milk, i.e., that is highly digestible protein, very low in carbohydrates with little antigenicity.

It will be understood that other ingredients are conventionally added to the diet, as shown in the above table. The lysine percentages must be carefully controlled, the amounts used approximating those shown in the above table. Additional ingredients such as fish meal, trace minerals including copper and selenium, vitamins, antibacterials and antibiotics are also added, as is well known to those skilled in the art.

Conventionally, the diet is fed on an ad libitum basis in the form of pellets or ground to form a meal, depending on the age of the pig. The appropriate form of the feed is well known to those skilled in the art, as are the feeding regimens, that is, the frequency and amount of diet fed to the animals.

Those skilled in the art may readily determine the amount of total feed at the various stages of pig development.

The following table provides the general ranges applicable to the various stages.

5

TABLE

	<u>Phase 1</u>	<u>Phase 2</u>	<u>Phase 3</u>
10 <u>Daily Intake (grams)</u>			
Broadly	150-700	400-900	600-1500
15 Preferred	300-500	500-800	800-1200

Most advantageously, the intake of the diet of the invention should average greater than 345 grams per day for the first two weeks, and average greater than 725 grams per day for the following three weeks. An average over 600 grams per day over the five weeks is also effective.

To demonstrate the efficacy of the instant invention attention is directed to the following example:

Example

25

One hundred eighty weanling pigs (22 ± 2 days of age, initial weight 6 kg) were used to show the effect of feeding nursery pigs L-carnitine on pig performance and carcass composition. The experimental design consisted of a 2 x 3 factorial arrangement with 0 or 1000 ppm L-carnitine fed in Phase 1 (0 to 2 weeks) combined with 0, 250 or 500 ppm L-carnitine in Phase 2 (3 to 5 weeks). Phase 1 diets contained 20% dried skim milk, 20% dried whey, 5% soybean oil and were formulated to contain 1.45% lysine. Phase 2 diets contained 10% dried whey, 5% soybean oil and were formulated to contain

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1.25% lysine. Six pigs at 0 and 1000 ppm carnitine level on day 14 and six pigs at 0 and 500 ppm carnitine level on day 35 (24 total) were sacrificed and ground to determine carcass composition. In Phase 1, L-carnitine increased ($P < .02$) feed intake (FI) and improved ($P < .08$) average daily gain (ADG), but had no effect on feed/gain (F/G). In Phase 2, and for the cumulative 5 week trial, increasing dietary L-carnitine improved (linear, $P < .06$) F/G and decreased (linear, $P < .05$) FI; however, ADG was not influenced. Carcass dry matter (DM) and crude protein (CP) were not influenced ($P > .15$) by dietary L-carnitine on day 14 or 25. Percent carcass lipid was not affected by dietary treatment on day 14; however, pigs fed 1000 ppm L-carnitine in Phase 1 had less ($P < .05$) daily fat accretion (DFA) on day 35 regardless of whether they were fed carnitine in Phase 2 or not. Based on the results of this experiment, L-carnitine addition reduces carcass fat when fed in Phase 1 and improves F/G when fed in Phase 2.

TABLE

<u>P1/P2^a</u>	<u>ADG, g</u> <u>0-2 wk^b</u>	<u>F/G</u> <u>0-2 wk</u>	<u>ADG, g</u> <u>3-5 wk</u>	<u>F/G</u> <u>3-5 wk^{c,d}</u>	<u>ADG, g</u> <u>0-5 wk</u>	<u>F/G</u> <u>0-5 wk^c</u>	<u>DM, %</u> <u>d 35</u>	<u>CP, %</u> <u>d 35</u>	<u>DFA, g</u> <u>d 35^e</u>
0/0	281	1.24	485	1.96	404	1.68	36.7	17.9	68.9
0/250	286	1.30	431	1.88	399	1.54	-	-	-
0/500	281	1.13	485	1.70	399	1.54	36.8	18.1	62.2
1000/0	318	1.17	480	1.92	417	1.66	35.4	18.3	39.1
1000/250	331	1.13	454	2.19	408	1.72	-	-	-
1000/500	286	1.19	454	1.78	386	1.59	36.4	17.5	47.1

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- a Phase 1/Phase 2 carnitine levels, ppm
b Carnitine effect (P<.08)
c Linear carnitine effect (P<.06)
d Quadratic carnitine effect (P<.02)
e Carnitine effect (P<.05)

What is claimed is:

1. A Phase 1 feed composition for starter pigs which comprises L-carnitine in admixture with a high nutrient density diet containing at least 30% milk products.
2. The composition of claim 1 wherein from 5 to 5000 ppm of L-carnitine are present.
3. The composition of claim 1 wherein from 250 to 2000 ppm of L-carnitine are present.
4. A feed composition for starter pigs comprising at least 5 ppm of L-carnitine and a milk-based high-nutrient density diet containing at least 30% milk products, 15% protein and 5% added fat.
5. A method of increasing the lean-to-fat ratio of swine which comprises feeding to swine at least in the nursery stage a high nutrient density diet containing L-carnitine and at least 30% of milk products.
6. The method of claim 5 wherein the high nutrient density diet contains at least 5 ppm of L-carnitine.
7. The method of claim 5 wherein the carnitine fed to the swine is, generally, in an inverse proportion to its weight.
8. A method of increasing the lean-to-fat ratio of a pig which comprises feeding to an early weaned pig, for a period of at least five weeks, a diet supplemented with L-carnitine.
9. The method of claim 8 wherein the carnitine level fed to said early weaned pig during the first two weeks is from 50 to 2000 ppm and during the next three weeks is reduced to

from 25 to 1000 ppm.

10. The method of claim 8 wherein the diet is a high nutrient density diet.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US92/00772

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) ³ According to International Patent Classification (IPC) or to both National Classification and IPC IPC (5): A61K 35/78, 47/00; A23K 1/00 US CL : 424/195.1, 548; 514/773, 909											
II. FIELDS SEARCHED <div style="text-align: center; border: 1px solid black; padding: 2px;">Minimum Documentation Searched⁴</div> <table style="width: 100%; border-collapse: collapse;"> <tr> <th style="width: 20%; border: 1px solid black; padding: 2px;">Classification System</th> <th style="border: 1px solid black; padding: 2px;">Classification Symbols</th> </tr> <tr> <td style="border: 1px solid black; text-align: center; padding: 5px;">U.S.</td> <td style="border: 1px solid black; padding: 5px;">424/195.1, 548; 514/773, 909</td> </tr> </table> <div style="text-align: center; border: 1px solid black; padding: 2px;">Documentation Searched other than Minimum Documentation to the extent that such Documents are included in the Fields Searched⁵</div>			Classification System	Classification Symbols	U.S.	424/195.1, 548; 514/773, 909					
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III. DOCUMENTS CONSIDERED TO BE RELEVANT ¹⁴ <table style="width: 100%; border-collapse: collapse;"> <tr> <th style="width: 10%; border: 1px solid black; padding: 2px;">Category*</th> <th style="border: 1px solid black; padding: 2px;">Citation of Document,¹⁶ with indication, where appropriate, of the relevant passages¹⁷</th> <th style="width: 10%; border: 1px solid black; padding: 2px;">Relevant to Claim No. ¹⁸</th> </tr> <tr> <td style="border: 1px solid black; text-align: center; vertical-align: top; padding: 5px;">A</td> <td style="border: 1px solid black; padding: 5px;">US, A, 3,810,994 (Wiegand) 14 May 1974, see entire document.</td> <td style="border: 1px solid black; text-align: center; vertical-align: top; padding: 5px;">1-10</td> </tr> <tr> <td style="border: 1px solid black; text-align: center; vertical-align: top; padding: 5px;">Y</td> <td style="border: 1px solid black; padding: 5px;">Newton et al, "1987 University of Georgia Swine Report, The University of Georgia College of Agriculture", Special Publication No. 44, published 1987. See entire document.</td> <td style="border: 1px solid black; text-align: center; vertical-align: top; padding: 5px;">1-10</td> </tr> </table>			Category*	Citation of Document, ¹⁶ with indication, where appropriate, of the relevant passages ¹⁷	Relevant to Claim No. ¹⁸	A	US, A, 3,810,994 (Wiegand) 14 May 1974, see entire document.	1-10	Y	Newton et al, "1987 University of Georgia Swine Report, The University of Georgia College of Agriculture", Special Publication No. 44, published 1987. See entire document.	1-10
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<div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p>* Special categories of cited documents:¹⁵</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 45%;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art</p> <p>"&" document member of the same patent family</p> </div> </div>											
IV. CERTIFICATION <table style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 50%; border: 1px solid black; padding: 5px;"> Date of the Actual Completion of the International Search² <div style="text-align: center; font-size: 1.2em;">25 June 1992</div> </td> <td style="width: 50%; border: 1px solid black; padding: 5px;"> Date of Mailing of this International Search Report² <div style="text-align: center; font-size: 1.2em;">01 JUL 1992</div> </td> </tr> <tr> <td style="border: 1px solid black; padding: 5px;"> International Searching Authority¹ <div style="text-align: center; font-size: 1.2em;">ISA/US</div> </td> <td style="border: 1px solid black; padding: 5px;"> Signature of Authorized Officer¹⁹ <div style="text-align: center;"> RALPH GITOMER </div> </td> </tr> </table>			Date of the Actual Completion of the International Search ² <div style="text-align: center; font-size: 1.2em;">25 June 1992</div>	Date of Mailing of this International Search Report ² <div style="text-align: center; font-size: 1.2em;">01 JUL 1992</div>	International Searching Authority ¹ <div style="text-align: center; font-size: 1.2em;">ISA/US</div>	Signature of Authorized Officer ¹⁹ <div style="text-align: center;"> RALPH GITOMER </div>					
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